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ABSTRACT

Sir John Cornforth's work on the synthesis of cholesterol and penicillamine, on the chemistry of oxazoles, the stereochemistry of the synthesis of alkenes, the synthesis of abscisic acid and of dibenzophospholes as mimics of enzyme action, is reviewed.

Keywords: cholesterol, penicillamine, oxazoles, the Cornforth rearrangement, alkene synthesis, abscisic acid, dibenzophospholes, mimics of enzyme action

1. Introduction

Sir John Cornforth made significant contributions both to organic synthesis and to the study of the mechanism and stereochemistry of enzyme reactions for which he was awarded the Nobel Prize in 1975. Although some aspects of his synthetic work were interwoven with his biosynthetic studies, other studies had purely chemical objectives. This article, which is the second of three, is concerned with this synthetic work. A third article describes Cornforth's biosynthetic studies.

Cornforth's work in this area spanned the best part of 60 years during which there were enormous changes to the repertoire of synthetic reactions that were available to chemists and to the understanding of the mechanism and stereochemical consequences of reactions together with the methods of separation and the use of spectroscopic methods in the identification of organic compounds. These are reflected in Cornforth's work and a comparison between his earlier and later papers provides many examples of these advances.

Cornforth summarised his views on synthesis in a lecture that he gave in Australia in 1992[1]. He saw synthesis as an art-form drawing parallels with both architecture and chess. In his synthetic work, it is possible to discern both architectural elegance and the strategic planning of a game of chess. He defined chemical synthesis as "the intentional construction of molecules by means of chemical reactions" and contrasted this with the development of new reactions which might have synthetic potential. Whilst at the start of his career, unambiguous synthesis was regarded as the ultimate proof of structure, however, as the years went by, he was more concerned with the purpose of synthesis to provide either a scarce biologically-active natural product or a compound with a specific property such as an isotopic label at a particular site, and finally with the potential of a synthetic compound to act as an enzyme mimic.

2. Steroid synthesis

Although cholesterol was widely available, the hormonal steroids could only be obtained from natural sources in very small amounts. Consequently, once their structures had been established in the early 1930s, their synthesis from more readily available materials was essential in order to explore their biological properties. Hence, in the mid 1930s, Robinson in Oxford had embarked on a study of their synthesis. The Cornforths joined this team in 1939 for their PhD research and, in 1951, Cornforth and Robinson reported[2] the synthesis of the non-aromatic hormonal steroid, epiandrosterone **6**. This represented one of the major synthetic achievements of the mid-20th century. Epiandrosterone possesses seven asymmetric centres and therefore has 128 possible stereoisomers. The object was to prepare just one of these in a pure form. The development of this successful synthesis and that of a parallel one by the Harvard chemist, R.B. Woodward, provided an understanding of many of the factors which control the

stereochemistry of ring junctions and paved the way for the synthesis of many polycyclic terpenoids in the 1950s and 1960s. Whilst the first stages of the Cornforth–Robinson synthesis were completed in Oxford in 1941–42[3-5], further progress was interrupted by the more pressing needs of war work on penicillin and the synthesis was not completed until after the war by Cornforth, who was by then working at the National Institute for Medical Research.

The strategy involved[6] the construction of rings B and C of the steroid from the dimethyl ether **1** of 1,6-dihydroxynaphthalene which possessed suitably placed oxygen functions to permit the addition of ring A and subsequently ring D. The initial target was a steroid degradation product, the Reich diketone **4** which not only provided a relay to augment the material for synthesis but also served to establish the stereochemistry of the synthetic material.

The naphthalene **1** was reduced[5] to 5-methoxy-2-tetralone **2** which was then methylated adjacent to the ketone and subjected to a Robinson ring-extension reaction to provide the tricyclic unsaturated ketone **3**. Reduction of the ring A double bond in **3** to a saturated ketone[7] followed by reduction of the second aromatic ring of the original naphthalene afforded two racemic hydroxy-ketones, which were isomeric at the B/C ring junction. These were separated but their stereochemistry was unknown. Both racemates were resolved and each of the four enantiomers was methylated adjacent to the ring C ketone and, after oxidation, four diketones were obtained. In 1947, one of these was found[8, 9] to be identical to the Reich diketone **4**. This compound had been obtained by degradation of the steroids and retained rings A, B and C. The identity established the stereochemistry of the synthetic product. This relay was then converted into another more readily available degradation product of cholesterol, the Koster–Logemann ketone **5** which was used to complete the construction of the five-membered ring D of epiandrosterone **6**. This was announced in 1951[2] at the same time as a synthesis using a different strategy was completed by Woodward[10]. The synthesis of cholesterol **7** required the introduction of the side chain, which was achieved in 1953[11].

What was remarkable about the Cornforth–Robinson synthesis was that it was completed without the aid of physical methods, which today we take for granted, without recourse to chromatographic methods of separation and with the use of a very limited range of synthetic reactions whose stereochemical consequences were, in the main, unknown at the time. Subsequent work has led to the commercial synthesis of the steroids. The Robinson ring extension reaction[12] has been widely used in the synthesis of polycyclic sesqui-, di- and tri-terpenoids. The partial reduction of a methoxynaphthalene by sodium in ethanol to the easily hydrolysed enol ether of a ketone has been acknowledged by fellow Australian Arthur Birch[13] as one of the papers that provided a precedent for the reduction of aromatic rings with sodium in liquid ammonia – a reaction which bears Birch's name. Birch was a colleague of Cornforth in the Dyson Perrins Laboratory, University of Oxford, in the 1940s.

3. Penicillin and penicillamine

One of the lessons of the First World War had been the importance of treating the bacterial infection of wounds. Consequently, the discovery of the antibiotic activity of penicillin was of great importance to the war effort of the Second World War. However, in the early 1940s not only was penicillin in short supply from natural sources but its structure was unknown. Hence there were major structural and synthetic efforts in this area in both Britain and the USA. After completing the earlier work on steroid synthesis for his PhD in 1941, Cornforth spent time on the synthesis of some potentially anti-malarial quinolines[14] before joining Robinson's penicillin team in 1943. There was a ban on the publication of this important wartime work and it was not described in full until the publication of a book on *The chemistry of penicillin* in 1949[15] to which Cornforth made a major

contribution. Individual pieces of work were described in confidential wartime reports submitted to the Medical Research Council's Committee on Penicillin Synthesis (CPS Reports).

Acid hydrolysis of penicillin **8** gave an amino acid, penicillamine **9** which was obtained in a crystalline form by Abraham in Oxford in October 1942 and in July 1943[16] this was shown, unexpectedly, to contain sulfur. In the light of some ambiguous determinations of *C*-methyl groups, there was uncertainty concerning its structure. Cornforth suggested that it was β,β-dimethylcysteine **9** in an Appendix (23 August 1943) to a CPS report from the Oxford group (14 August 1943)[17] and within six weeks in the autumn of 1943, he had not only synthesised this structure but resolved it and shown that this amino acid belonged to the unusual D series[18]. The structure of D-penicillamine accounted for a significant portion of the core of the penicillins. Subsequently D-penicillamine has been shown to have a number of other important therapeutic properties including the treatment of Wilson's disease[19, 20], lead poisoning and as an anti-rheumatic drug.

There was considerable discussion of the overall structure of penicillin. Robinson proposed a thiazolidine:oxazolone structure **10** whilst Abraham and Chain and independently, Woodward, proposed the now accepted β-lactam **8**.[21] The structural controversy was not resolved[22] until the X-ray work of Dorothy Hodgkin in May 1945. Since penicillin was in short supply in 1944, oxazolones became a target for synthesis with the objective[23, 24] of coupling them with penicillamine to synthesise possible 'penicillin-like' structures with antibiotic activity.

4. Oxazole chemistry

Since it was known that penicillamine formed a thiazolidine by condensation with a ketone, an oxazole possessing an aldehyde at C-4 was a suitable component for the construction of a thiazolidine:oxazole, which at the time (1944) was under consideration as a possible structure for penicillin. In an attempt to prepare such an aldehyde by the catalytic reduction of an acid chloride (Rosenmund reduction), 2-pentyl-5-ethoxyoxazole-4-carboxylic acid was treated with phosphorus pentachloride but, instead of the acid chloride, the ethyl ester of 2-pentyl-5-chlorooxazole-4-carboxylic acid was obtained. Cornforth recognised that this reaction was an example of a more general thermal rearrangement of 4-carbonyl-substituted oxazoles **11** → **12**, now known as the Cornforth rearrangement[25]. Discussions with Cornforth's Oxford University friend and colleague Michael Dewar led to the suggestion that the mechanism of this rearrangement is *via* opening and closure of the oxazole ring[25,26], and this is now generally accepted, although the detailed nature of the intermediates has yet to be confirmed. The Cornforth rearrangement has been utilised for the synthesis of less readily available oxazoles such as 5-aminooxazoles.

This work on oxazoles led Cornforth to make a number of significant contributions to their chemistry including a new synthesis of this ring system as well as that of imidazoles. He also reported the synthesis of a number of substituted oxazoles and related topics[27-34]. For example, the ready cleavage of the oxazole ring provided a route to acylamidomalondialdehydes which were difficult to synthesise by other means. As a result of considering the mechanism of Emil Fischer's synthesis of 2,5-diaryloxazoles, Cornforth was able to widen its scope to the preparation of alkyl derivatives.

Cornforth returned to oxazole chemistry at various stages in his scientific career. Thus, in 1990, he reported[35] an efficient synthesis of 4-methylpyrrole-2-carboxylate and 3-methylpyrrole using oxazole chemistry, **13** → **14**. In the course of this study, he uncovered a novel thermal isomerisation of an oxazole to a pyrone **15**. This led Cornforth to re-examine[36] the condensation of salicylaldehyde with hippuric acid, a reaction which would be part of the conventional synthesis of an amino acid. There were 18 reports in the literature of the formation of the alleged oxazolone **16** in this reaction, all of

which Cornforth showed to be erroneous ('the comedy of errors'). He prepared the authentic material **16** and showed that many of the previous products were in fact a rearrangement product, the benzoylaminocoumarin **17**. He commented in the paper that 'one published error breeds others.'

5. Chemical work at the National Institute for Medical Research

Apart from completing work on the synthesis of the steroids and on the chemistry of oxazoles, Cornforth made a significant chemical input into a number of programmes of medical importance whilst he was at the National Institute for Medical Research (NIMR). These included studies of anti- tubercular compounds[37, 38], the synthesis of tryptophan metabolites[39] and *N*-acetylneuraminic acid[40].

The discovery at the Mayo Clinic in Rochester, Minnesota, in 1949 of the effect of cortisone in alleviating the symptoms of rheumatoid arthritis, stimulated considerable research in the following years into methods for obtaining the relatively rare C-11 oxygenated steroids. In 1951, Cornforth showed[41] that the 12-keto steroidal sapogenin, hecogenin **18** could be obtained in quantity as a by-product from the large-scale manufacture of sisal fibre and, in 1953, he published[42] a route which proceeded in good yield, for transposing the oxygen atom from C-12 to C-11. Cornforth's methodology was based on the stereochemistry of the reactions of epoxides. This was at a time when the stereochemistry of many reactions and in particular their conformational analysis, was attracting considerable attention. These were concepts which Cornforth later exploited in the stereospecific syntheses of alkenes and labelled mevalonates.

Cornforth's work on the biosynthesis of squalene and cholesterol in collaboration with George Popják began in 1948 at the NIMR and, as a consequence, he carried out a number of investigations into the chemistry of cholesterol and into the synthesis of labelled biosynthetic intermediates. These are described in the accompanying article on biosynthetic studies. However, one important aspect of this work which was reported in 1954[43] involved the degradation of ring D and the side chain of cholesterol to a fragment retaining the chiral centre at C-20. This fragment was also synthesised from (+)-citronellal which had in turn been related to (+)-methylsuccinic acid and thence to D-glyceraldehyde. This inter-relationship established the absolute stereochemistry of cholesterol.

6. Alkene synthesis

All-*trans*-squalene plays a central role as an intermediate in the biosynthesis of the sterols. Squalene occurs naturally in shark liver oil and its structure contains a number of trisubstituted double bonds. The study of its role in sterol biosynthesis required a stereospecific chemical synthesis. At the time of Cornforth's work on this biosynthesis, there was a dearth of methods for constructing a trisubstituted double bond of established regiospecificity. Consequently, Cornforth developed[44] a general method for the stereoselective synthesis of alkenes based on an elimination reaction of an α-halohydrin which had, in turn, been obtained from an addition reaction to an α-haloketone. In defining the stereochemistry of the halohydrin, he considered that the repulsive interaction between a carbonyl group and an adjacent chlorine would lead them to take up an anti-conformation as in **19**. This would then determine the stereochemistry around the carbonyl group and in particular the direction of nucleophilic addition to the carbonyl group. This Cornforth model for rationalising and predicting the stereochemistry of nucleophilic addition to a carbonyl group with an adjacent stereocentre containing a polar group has been the subject of considerable discussion[45] particularly in the light of other proposals such as the Felkin–Ahn models.

Cornforth observed that addition of a Grignard reagent such as ethylmagnesium bromide to 3-chlorobutan-2-one **20** gave the diastereoisomer **21** with 85% stereoselectivity. Treatment of the

chlorohydrins with base gave the epoxide **22**. This was then transformed *via* an iodohydrin **23** to an alkene of defined geometry **24**. The method was extended[46] to the synthesis of all-*trans*-squalene. As part of this work Cornforth also examined[47] the formation of iodohydrins and thence epoxides from alkenes.

7. Abscisic acid

The onset of dormancy and leaf fall is an important part of the life-cycle of a plant. Abscisic acid **25** is a plant hormone which mediates these stages[48]. However, it is present in very small amounts in plants. Cornforth was involved in establishing the identity of preparations from various plants[49], determining the stereochemistry of abscisic acid[50] and in confirming its structure by synthesis. In his first synthesis[51], abscisic acid was obtained from dehydro-β-ionone **26**. An interesting aspect of this synthesis was the photo-sensitised addition of oxygen to a cyclic diene and the cleavage of the resultant epidioxide with base to generate the γ-hydroxy-αβ-unsaturated ketone of abscisic acid. This route was used to prepare labelled material[52]. A later stereospecific route[53] utilised 6-chloro-4-methylpyran-2-one **27** to provide the *cis* geometry of the unsaturated acid that characterises the side chain of abscisic acid. These studies not only placed the chemistry of abscisic acid on a firm footing but have also provided the stimulus for a number of other syntheses and for an examination of its biosynthesis.

8. Models of enzyme action

Having spent many years studying the stereochemical consequences of substrate:enzyme interactions and the efficiency of these processes, Cornforth was attracted to the idea of selecting a chemical reaction and considering ways of accelerating it as an enzyme might. The object was to translate these ideas into the chemical structure of a catalyst which might fulfil these objectives. In attempting to devise a catalyst which might have some of the properties of an enzyme, such as its selectivity and efficiency, Cornforth chose[54] to examine as a reaction the hydration of an alkene.The objective was to develop a stable, easily prepared and efficient catalyst which would work at room temperature in an aqueous environment and which might have commercial application. Although it was expected that the catalyst would be water soluble, in order to favour the binding of an alkene, it had to possess a hydrophobic cleft containing a suitable acidic group to protonate an alkene. A phosphinic acid had about the right pK for this purpose and consequently the target was a dibenzophosphole **28** in which the benzene rings provided not only the side of the cleft but also the means of adding substituents to vary the pK of the phosphinic acid and to add groups which might provide water solubility and possibly introduce chirality.

Initial unsuccessful attempts to synthesise the dibenzophosphole by coupling a bisdiphenylphosphinic acid **29** suggested[55] that the best approach would be to create a quaterphenyl and then to introduce the phosphinic acid moiety. Cornforth developed[56, 57] a useful coupling of 1,3-dinitrobenzene **30** with aryl iodides **31** using copper *tert*-butoxide in pyridine which provided a convenient new method for preparing 2,6-dinitrodiphenyls (*e.g.* **32**). 2-Arylation of 1,3-dinitrobenzene using this procedure, followed by displacement of a nitro group by a methoxyl group and iodination *para* to the methoxyl, gave a 3-aryl-4-methoxy-2-nitroiodobenzene **33**. An Ullmann copper coupling of this aryl halide then gave the quaterphenyls **34**. The phosphinic acid was then introduced[58-61] by reduction of the nitro group to an amine, diazotisation and iodination. Treatment with butyl lithium and reaction with methyl or ethyl dichlorophosphite led to the introduction of the required group **35**. However, the synthesis of the more heavily substituted compounds required an alternative approach based on neighbouring group participation between the rings in order to achieve

selectivity[62, 63]. The eventual outcome was the synthesis[64] of two phosphinic-polyphosphinic acids (*e.g.* **36**) containing respectively three and four water-solubilising phosphonomethyl groups. These catalysts were soluble in water at a pH 3–4 and they catalysed the hydration of 2-methylpropene to *tert*-butanol approximately three times more efficiently than a toluene-*p*-sulfonic acid solution of comparable acidity.This result, whilst establishing the principle, suggested that in order to reach useful levels of catalysis, the cleft in which the phosphinic acid function resided, would need to be redesigned.

Cornforth's synthetic work reflects an elegance in its planning and a thoroughness in its execution which, coupled with an understanding of the reaction mechanisms involved, enabled him to overcome many obstacles and achieve a successful outcome. His command of the literature and attention to detail is reflected in the number of times that he was able to correct mistakes by earlier workers and to build on chance observations to develop novel chemistry.

References

1. Cornforth, Sir J.W. (1993) *Aust. J. Chem.*, **46**, 157-170.
2. Cardwell, H.M.E., Cornforth, J.W., Duff, S.R., Holtermann, H and Robinson, R. (1951) *Chem. Ind. (London)*, 389-390.
3. Cornforth, J.W., Cornforth, R.H. and Robinson, R. (1942) *J. Chem. Soc.*, 682-684.
4. Cornforth, J.W. and Robinson, R. (1942) *J. Chem. Soc.*, 684-689.
5. Cornforth, J.W., Cornforth, R.H. and Robinson, R. (1942) *J. Chem. Soc.*, 689-691.
6. Cornforth, J.W. (1955) *Prog. Org. Chem.*, **3**, 1-43.
7. Cornforth, J.W. and Robinson, R. (1946) *J. Chem. Soc.*, 676-679.
8. Cornforth, J.W. and Robinson, R. (1947) *Nature (London)*, **160,** 737.
9. Cornforth, J.W. and Robinson, R. (1949) *J. Chem. Soc.*, 1855-1865.
10. Woodward, R.B., Sondheimer, F., Taub, D., Heusler, K. and Mohamore, W. (1951) *J. Am. Chem. Soc.*, **73**, 2403.
11. Cardwe1l, H.M.E., Cornforth, J.W., Duff, S.R., Holtermann, H. and Robinson, R. (1953) *J. Chem. Soc.*, 361-365.
12. Du Feu, E.C., McQuillin, F.J. and Robinson, R. (1937) *J. Chem. Soc.*, 53-58.
13. Birch, A.J. In: Golding, B.T. (ed.) *John Warcup Cornforth, selected research papers with commentaries*, p.15. Pergamon Press, Elsevier, l992.
14. Cornforth, J.W. and Cornforth, R.H. (1948) *J. Chem. Soc.*, 93-97.
15. Clarke, H.T., Johnson, J.R. and Robinson, R. (eds) *The chemistry of penicillin.* Princeton University Press, New Jersey, 1949.
16. Abraham, E.P.(1987) *Nat. Prod. Rep.*, **4**, 41-46.
17. Abraham, E.P., Baker, W., Chain, E. and Robinson, R. (1943) *CPS Report*, PEN. 91, 14 August.
18. Abraham, E.P., Chain, E., Baker, W., Cornforth, J.W., Cornforth, R.H. and Robinson, R. (1943) *CPS Report*, PEN. l00, 4 October.
19. Purchase, R. (2013) *Sci. Prog.*, **96,** 1-18.
20. Purchase, R. (2013) *Sci. Prog.*, **96,** 213-223.
21. Abraham, E.P., Baker, W., Chain, E. and Robinson, R. (1943) *CPS Report*, PEN. 103, 22 October.
22. Crowfoot, D., Bunn, C.W., Rodgers-Low, B.W. and Turner, J. (1949) In: Clarke, H.T., Johnson, J.R. and Robinson, R. (eds) *The chemistry of penicillin*, pp. 310-367. Princeton University Press, New Jersey.
23. Cornforth, J.W., Cornforth, R.H., Abraham, E.P., Baker, W., Chain, E. and Robinson, R. (1944) *CPS Report* PEN 58, 1 May.
24. Cornforth, J.W., Cornforth, R.H., Abraham, E.P., Baker, W., Chain, E. and Robinson, R. (1945)

CPS Report PEN 492 11 May.
25. Cornforth, J.W. (1957) In: Elderfield, R.C. (ed.), *Heterocyclic compounds*, Vol. 5, pp. 298-417. John Wiley and Sons, New York.
26. Dewar, M.J.S. (1949) The electronic theory of organic chemistry, p. 87. Clarendon Press, Oxford.
27. Cornforth, J.W. and Cornforth, R.H. (1947) *J. Chem. Soc.*, 96-102.
28. Cornforth, J.W. and Huang, H.T. (1948) *J. Chem. Soc.*, 1960-1964.
29. Cornforth, J.W. and Huang, H.T. (1948) *J. Chem. Soc.*, 1969-1971.
30. Cornforth, J.W. and Huang, H.T. (1948) *J. Chem. Soc.*, 1964-1969.
31. Cornforth, J.W., Fawaz, E., Goldsworthy, L.J. and Robinson, R. (1949) *J. Chem. Soc.*, 1548-1553.
32. Cornforth, J.W. and Cornforth, R.H. (1953) *J. Chem. Soc.*, 93-98.
33. Cornforth, J.W. and Cornforth, R.H. (1949) *J. Chem. Soc.*, 1028-1030.
34. Cornforth, J.W. and Cookson, E. (1951) *J. Chem. Soc.*, 1085-1088.
35. Cornforth, Sir John and Du, M.H. (1990) *J. Chem. Soc., Perkin Trans.1*, 1459-1462.
36. Cornforth, Sir John and Du, M.H. (1991) *J. Chem. Soc., Perkin Trans.1*, 2183-2187.
37. Cornforth, J.W., Hart, P.D.A., Rees, R.J.W. and Stock, J.A. (1951) *Nature (Lond.)*, **168**, 150.
38. Cornforth, J.W., Hart, P.D.A., Nicholls, G.A., Rees, R.J.W. and Stock, J.A. (1955) *Brit. J. Pharmacol.*, **10**, 73-86.
39. Cornforth, J.W., Cornforth, R.W., Dagliesh, C.E. and Neuberger, A. (1951) *Biochem. J.*, **48,** 591-597.
40. Cornforth, J.W., Firth, M.E. and Gottschalk, A. (1958) *Biochem. J.*, **68**, 57-61.
41. Callow, R.K., Cornforth, J.W. and Spensley, P.C. (1951) *Chem. Ind. (Lond.)*, 699.
42. Cornforth, J.W., Osbond, J.W. and Phillipps, G.H. (1954) *J. Chem. Soc.*, 907-912.
43. Cornforth, J.W., Youhotsky, I. and Popják, G.J. (1954) *Nature (Lond.)*, **173**, 536-538.
44. Cornforth, J.W., Cornforth, R.H. and Mathew, K.K. (1959) *J. Chem. Soc.*, 112-117.
45. O'Brien, A.G., (2011), *Tetrahedron*, **67**, 9639-9667.
46. Cornforth, J.W., Cornforth, R.H. and Mathew, K.K. (1959) *J.Chem.Soc.*, 2539-2547.
47. Cornforth, J.W. and Green, D.T. (1970) *J. Chem. Soc. (C)*, 846-849.
48. Milborrow, B.V. (2001) *J. Exp. Bot.*, **52**, 1145-1164.
49. Cornforth, J.W., Milborrow, B.V. and Ryback, G. (1966) *Tetrahedron, Suppl. B, Part II*, 603-610.
50. Cornforth, J.W., Draber, W., Milborrow, B.V. and Ryback, G. (1967) *Chem. Commun.*, 114.
51. Cornforth, J.W., Milborrow, B.V.and Ryback, G. (1965) *Nature (Lond.)*, **206,** 715.
52. Cornforth, J.W., Mallaby, R. and Ryback, G. (1968) *J. Chem. Soc. (C)*, 1565-1568.
53. Cornforth, Sir John, Hawes, J.E. and Mallaby, R. (1992) *Aust. J. Chem.*, **45**, 179-185.
54. Cornforth, Sir John (1978) *Proc. R. Soc. London, Ser. B.*, **203**, 101-117.
55. Cornforth, Sir John, Cornforth, Lady R.H., and Gray, T. (1982) *J. Chem. Soc., Perkin Trans 1*, 2289-2297.
56. Cornforth, Sir John, Sierakowski, A.F. and Wallace, T.W. (1979) *J. Chem. Soc., Chem. Commun.*, 294-295.
57. Cornforth, Sir John, Sierakowski, A.F. and Wallace, T.W. (1982) *J. Chem.Soc., PerkinTrans.1*, 2299-2315.
58. Cornforth, Sir John, Ridley, D.D., Sierakowski, A.F., Uguen, D., Wallace, T.W. and Hitchcock, P.B. (1982) *J. Chem. Soc., Perkin Trans. 1*, 2317-2331.
59. Cornforth, Sir John, Ridley, D.D., Sierakowski, A.F., Uguen, D. and Wallace, T.W. (1982) *J. Chem. Soc., Perkin Trans.1*, 2333-2339.
60. Buttrus, N.H., Cornforth, Sir John, Hitchcock, P.B., Kumar, A. and Stuart, A.S. (1987) *J.Chem. Soc., Perkin Trans.1*, 851-857.

61. Cornforth, Sir John, Kumar, A. and Stuart, A.S.(1987) *J. Chem. Soc., Perkin Trans.1*, 859-866.
62. Cornforth, Sir John and Robertson, A.D. (1987) *J. Chem. Soc., Perkin Trans.1*, 867-870.
63. Cornforth, Sir John, Huguenin, L.M. and Wilson, J.R.H. (1987) *J. Chem. Soc., Perkin Trans.1*, 871-875.
64. Cornforth, Sir John (1996) *J. Chem. Soc., Perkin Trans.1*, 2889-2893.